Br. J. clin. Pharmac. (1987), **23**, 195–198

Benoxaprofen—adverse reactions and monitoring in general practice

P. G. NEWRICK*
Frenchay Hospital, Bristol BS16 1LE

D. BAINTON†
Bristol and Weston Health Authority, 10 Marlborough Street, Bristol BS1 3NP

1 We report on the pattern of use of benoxaprofen (Opren) in a single group practice for a period which included the complete clinical life of the drug.
2 One hundred and seventy-two patients of the 6495 practice patients had been prescribed benoxaprofen, but 55% had only a small exposure (< 20 g). Recorded adverse reactions, of which none was serious, appeared in 25 patients.
3 Most were taking benoxaprofen for osteoarthritis (53%) or non-specific musculoskeletal pain (39.9%).
4 The issue of a prescription was not recorded in 19.6% of cases and 88% were on additional drugs.
5 Greater precision in record-keeping is required to avoid problems similar to the experience with benoxaprofen.

Keywords benoxaprofen general practice adverse reactions prescription event recording

Introduction

Benoxaprofen (Opren), initially available in May 1980 was marketed for prescribing by general practitioners in October 1980. In August 1982, it was withdrawn from use following a number of deaths and other side-effects which were attributed to the drug.

Methods

One of us (DB) was receiving, from a local three doctor general practice, carbon copies of every prescription issued by the practice as part of another study. It was possible therefore to identify every patient who had received a script(s) for benoxaprofen, within the defined population of the practice. The original study spanned the entire clinical life of the drug from May 1980 to August 1982. With the agreement of the three general practitioners (GPs) the records of every patient exposed to benoxaprofen were read in their entirety by one of the authors (PGN) and a structured proforma completed to include the following information: Sex of patient and age at first script, Date of first script, Total exposure, Condition for which the drug was used and how diagnosis was established, Concurrent drug treatment, Numbers of scripts not recorded in

*Present address and address for correspondence: Diabetes Research Registrar, Floor P, Royal Hallamshire Hospital, Sheffield S10 2JF
†Present address: Community Medicine Specialist (Evaluation), Huddersfield Health Authority, Huddersfield HD4 5RH

the notes, Any record of adverse events associated with benoxaprofen.

Results

One hundred and seventy-two patients (44 males, 128 females) of the 6495 practice list (as at July 1981) had taken benoxaprofen at some time, and had received a total of 426 prescriptions. Complete details were not available for four patients because they had left the area. A histogram of age at first script (median 67 years) is shown in Figure 1. Benoxaprofen was prescribed by the practice for 22 months (October 1980 to July 1982). Its use was so rapidly taken up that 60% of the patients received their initial prescription in the first 8 months. The peak month for new prescriptions of benoxaprofen was December 1980, only 2 months after the drug became available for prescription by GPs.

The pattern of drug exposure was similar for males and females. The mean number of scripts per person was 2.5. The mean duration of exposure to the drug was 82 days and mean total dose of benoxaprofen taken was 49 g. All patients were taking 600 mg benoxaprofen per day, the manufacturer's recommended dosage. Figure 2 shows a histogram of total dose of benoxaprofen prescribed. The overall pattern of prescribing of benoxaprofen by the practice is displayed graphically in Figure 3. Ten patients were taking the drug after the second U.K. report of deaths associated with its use was published.

Ninety-four (55%) of the patients took 18 g or less of benoxaprofen—that is, equivalent to a single 30 day course at 600 mg day^{-1}.

Benoxaprofen was prescribed for osteoarthritis in 89 cases (chiefly of knee and hip), for non-specific symptoms in 67 (e.g. low back pain, aching legs, sore elbows) and for inflammatory joint disease in 12 (11 cases of rheumatoid arthritis and one case of pseudogout). The diagnosis was made in the following ways: GP clinical diagnosis alone (36%), or supported by a GP blood test (5%) or X-ray (18%), or blood test and X-ray (6%). The diagnosis was made in a hospital clinic in 35% of patients, of these three-quarters were already using benoxaprofen prior to their hospital appointment.

One hundred and fifty-one (88%) patients were taking other drugs during the time they were on benoxaprofen—chiefly antibiotics, analgesics and diuretics. Six patients were on an additional non-steroidal anti-inflammatory drug (NSAID) concurrently, 10 patients had started benoxaprofen as initial treatment and the remainder had tried one or more similar drugs in

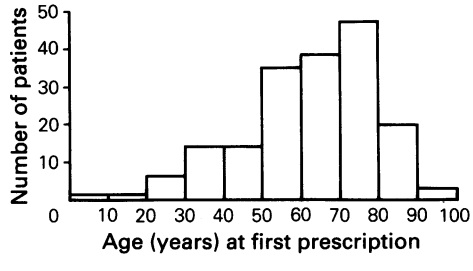

Figure 1 Age at first prescription for benoxaprofen.

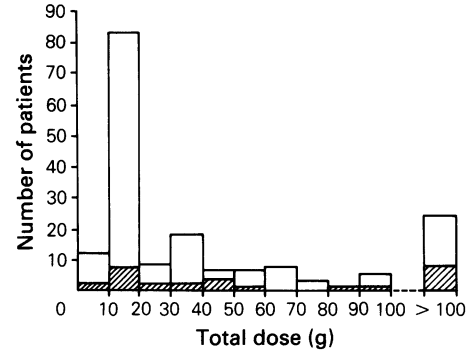

Figure 2 Total dose of benoxaprofen. ▨ Number of patients experiencing an ADR, □ number of patients without an ADR.

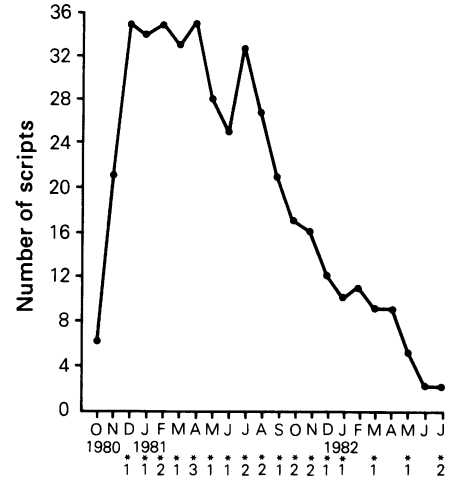

Figure 3 Benoxaprofen prescriptions by month of issue. *, Recognition of ADR by doctor (with numbers below).

the past in an attempt to find the most satisfactory agent.

Of the 168 patients for which full details were available, 25 experienced an adverse drug event during benoxaprofen treatment. These events were strongly suspected to be true adverse drug reactions (ADRs) to benoxaprofen on clinical grounds, and in all cases follow-up notes showed resolution of symptoms on stopping benoxaprofen. Direct causality was not proved conclusively and re-challenges were not attempted. Ten patients (eight during the summer months of May–August) developed photosensitivity after mean treatment of 184 days, and the remainder suffered other cutaneous (six cases) and gastrointestinal side effects (nine cases—one of melaena secondary to duodenitis in a 67 year old female with no previous gastrointestinal disease or NSAID usage). This represents a crude incidence figure of 0.66 adverse reactions per patient year of treatment. However, because all three doctors stopped writing prescriptions for those who experienced an ADR or who derived no benefit, the risks of developing an ADR whilst taking the drug have been calculated using the life-table method (Cutler *et al.*, 1958). This allows the risk to be expressed in relation to the duration of exposure and is displayed graphically in Figure 4.

The issuing of a benoxaprofen script was not recorded on 98 occasions in the notes of 33 (19.6%) patients. Of these patients, eight had an ADR. These latter patients had been issued with a mean of 11 scripts (range 3–16) and had an ADR rate of twice that of the remainder of the group. In six patients there was no mention of benoxaprofen in the records at all (four cases had one prescription; one case had two; and one case had three not recorded).

The characteristics of those patients with an ADR were not different for age or diagnosis but they had been on treatment longer and thus taken a significantly increased total dose of drug ($P < 0.001$). Many of the patients exposed to benoxaprofen were over 70 years and the experience of this elderly group is contrasted with the younger patients in Table 1. All 25 patients with an ADR were on other drugs concurrently (not other anti-inflammatory agents).

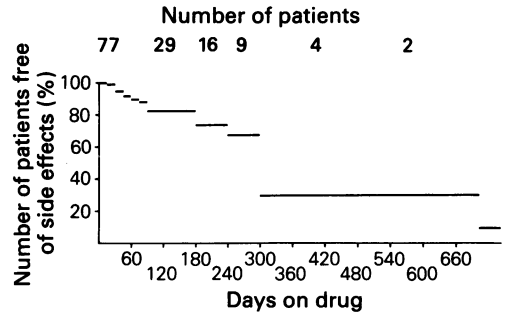

Figure 4 Cummulative risk of reaction to benoxaprofen.

Discussion

Post-marketing surveillance of new drugs will always be required because trial groups are either too small to identify an ADR, or differ in some way from the patient population who will ultimately receive the drug. For instance, the general practice population receiving benoxaprofen was elderly, yet taking a standard dose and frequently using it for ill-defined non-specific symptoms which cannot be recommended for any new drug. Our results, however, do not support the view that the elderly are at risk because of their age but rather because of prolonged treatment. The explosive uptake of benoxaprofen in the first few months after marketing is well shown with 60% of patients receiving their initial prescription in the first 8 months. This is a situation which gives rise to potential hazards in which any delay in recognising ADRs results in many more patients being exposed to risk than is necessary.

Traditional GP records are one potential 'hard' source of medical data that can, through prescription event monitoring (Inman, 1981), be used to increase ADR detection by the recording of clinical events occurring in patients on drugs. However, no matter how sophisticated the methods of data collection, the results are devalued if the relevant details have not been recorded by the GP. Our study deals with relatively small numbers only, and yet the shape of the prescribing curve (Figure 3) and the rates of ADRs parallel the information available to the

Table 1 Benoxaprofen experience in the elderly

Age (years)	*Number*	*Mean duration of benoxaprofen treatment (days)*	*Number of adverse reactions*
70–94	67	116	10
9–69	101	59	15

CSM (verbal communication Dr Weber, CSM). This promises grounds for optimism that smaller, more local surveillance schemes might yield information on all but extremely rare ADRs.

Inman (1981) has coherently argued the case for post-marketing surveillance of new drugs. Benoxaprofen is now of historical interest only but methods of surveillance are unchanged. Greater precision in record-keeping remains essential if similar problems are to be avoided in the future.

We gratefully acknowledge the help and co-operation of Drs C. A. E. Hoyte, J. H. C. Morgan and J. S. Rees of Corbett House Surgery, Bristol for allowing us to examine their prescribing area, and Mr T. B. Dowell for help with data processing.

References

Cutler, S. J. & Ederer, F. (1958). Maximum utilisation of the life-table method in analysing survival. *J. chronic Dis.*, **8**, 699–712.

Inman, W. H. W. (1981). Post-marketing surveillance of adverse drug reactions in General Practice. 2: Prescription event monitoring at the University of Southampton. *Br. med. J.*, **282**, 1216–1217.

(Received 12 June 1986, accepted 1 October 1986)